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# DEVELOPMENTAL PATTERNING OF NEURAL CIRCUITS*

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The present audience is familiar with the essential features of the histogenesis and the gross morphogenesis of the nervous system, excellent descriptions of which are available in our current textbooks of embryology. With this background we may turn our attention directly to that specialized phase of neurogenesis that deals with the outgrowth of the developing nerve fibers and the establishment of their terminal connections.

With few exceptions, the elongating processes of the developing neurons, insofar as they survive, eventually acquire intimate associations with other cells. The majority, as you know, form synaptic junctions with fellow neurons. Others form endorgan connections of diverse types in the periphery. The patterns of neuronal hook-ups thus formed in the course of ontogeny need to be highly selective and elaborately designed in order to mediate the functions which the developed nervous system must later carry out. In no other organ system of the body do the relations of the individual cell units to one another count so much. The vital importance of precise patterning is well illustrated in the abnormal and often bizarre functional effects (Sperry, 1945c, 1947b) that follow any surgical or accidental rearrangements of the normal neuronal associations.

The ensuing discussion is concerned primarily with the question of how this orderly patterning of fiber connections is achieved in development. Reducing our problem to its simplest terms, it may be stated as follows: How do the outgrowing fibers of the developing neurons manage to acquire their proper endorgan connections in the periphery and their proper synaptic junctions in the ganglia and nerve centers? The emphasis here is on the word "proper" with special regard for the *selectivity* of neuronal connections. From the standpoint of the function of the developed nervous system, this constitutes one of the most important and interesting phases of neural growth. It certainly is one of the most complicated and refined steps of neurogenesis, and also one about which we yet have a great deal to learn.

One of the main issues which has arisen in this field has been the question of the extent to which the neuronal associations are patterned by function, i.e., by some process akin to learning or conditioning, involving experience, trial and error, etc., and the extent, on the other hand, to which the integrative linkages are organized directly in the growth process itself, prior to and independently of function. The problem of the degree to which our brain functions, i.e., our intelligence, our skills, talents, temperaments, etc. are inherently predetermined, is an old one and has widespread practical import.

In the past it has been predominantly assumed that the functional factors are primary. The integrative circuits of the brain, it has been reasoned, are much too elaborate and complicated in their design and too delicate and precise in their functional adaptation to be constructed by developmental forces alone without aid of functional adjustment. Hypotheses have been formulated along various lines in an attempt to account for the manner in which the neural patterns might become organized through experience. According to one proposal, the neural pathways were supposed to be laid down at first in a diffuse, equipotential manner. Subsequent activity was then presumed to channel out certain adaptive routes in the matrix making these prepotent over the less adaptive pathways. Another interpretation held that synaptic formation itself is constantly influenced by the functional adaptiveness of the completed circuits. Those synapses forming circuits which happen to have adaptive value are somehow reinforced in the growth pro-

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cess whereas those which happen not to be adaptive are resorbed, or atrophy and degenerate. Perhaps the most widely circulated hypothesis has been that of "neurobiotaxis." In this theory it is assumed that the direction of growth and termination of the developing nerve fibers are influenced by electrical potentials generated in neighboring fiber tracts and nuclei during activity. Associations are supposed to be established between tracts and nuclei which happen, in the course of experience, to be activated simultaneously or in close succession.

In contradiction to the viewpoint that function is primary, experiments we have been conducting in recent years on the patterning of synaptic linkages (Sperry, 1941-1950) have consistently supported the opposing contention that the basic integrative plan of the nervous system is organized by developmental forces *per se*. The results leave no doubt that the growth process itself is entirely capable of laying down highly refined integrative patterns, quite independently of functional adaptation. The data, furthermore, are beginning to furnish some insight into the nature and general plan of the developmental forces responsible for this inherent patterning of the integrative pathways.

Before discussing these experiments, it may be well to point out that anyone wishing to study the formation and patterning of synaptic connections is pretty well restricted in the type of experimental material that can be used. There are certain advantages to working with the *regeneration* of synaptic connections in the developed organism. All the evidence so far indicates that the factors responsible for synaptic patterning in regeneration are essentially the same as those operative in initial development. However, the capacity of the developed nervous system to regenerate central synaptic relations appears to be limited for practical purposes to the amphibians and lower vertebrates. Study of the *initial development* of synaptic endings in ontogeny, on the other hand, is likewise most easily conducted in the amphibians where the embryo is readily accessible from the beginning and where the behavioral effects can be determined in early larval stages. As with other phases of experimental embryology, therefore, most of our information has come from the amphibians, i.e., from the frogs, toads, newts, and salamanders.

The nature of the experimental evidence and its implications may best be illustrated, perhaps, by a brief consideration of some of the investigations dealing with the patterning of synaptic connections in the visual pathways. You recall that the fibers connecting the eye and brain have their cell bodies located in the ganglion cell layer of the retina. During development optic axons grow centripetally in the optic nerve to terminate mainly, in the amphibians, in the optic tectum of the mesencephalon. The central connections of the optic fibers must match and reflect the spatial interrelations of all the retinal points from which the fibers arise. This is necessary for accurate visual perception of the direction and speed of movement and for the perception of spatial relationships. Functionally, each retinal point must acquire its own spatial "sign."

It is conceivable that the required pattern of central connections might be attained in development through an orderly timing of fiber ingrowth with mere mechanical guidance of the individual axons. For example, might not the nerve be built in successive concentric layers? The various possibilities of this sort are easily tested by determining the functional effects of optic nerve regeneration in which there is involved a complete disruption of any order in the timing and spatial arrangement of fiber ingrowth. In answer to our question, it has been found that optic nerve regeneration in adult frogs, toads, newts, salamanders, and various species of fishes consistently leads to an orderly recovery of the normal perception of movement and spatial relations. Histological checks have shown that this occurs despite a haphazard disorganization of fibers in the nerve scar. On the basis of such results it has been possible to eliminate mechanical guidance and timing of fiber ingrowth as the responsible organizing factors.

Another way in which the proper pat-

terning of central connections might conceivably be achieved is through functional adjustment. Function could operate in regeneration as well as in initial development through some mechanism such as neurobiotaxis, trial and error channelling, or selective synaptic reinforcement as mentioned above. Possibilities along these lines have been tested by combining transection and regeneration of the optic nerve with 180 degree rotation of the eyeball. Rotation of the eye alone, leaving the nerve connections intact, have been found to cause a reversal and misdirection of visual responses that persists indefinitely in these lower vertebrates without correction by reeducation. When eye rotation is combined with optic nerve section, we find that the visual responses recovered after regeneration are systematically reversed in exactly the same way.

If only one axis of the retina is inverted, as after contralateral transplantation of the eye, the recovered visual responses are correspondingly misdirected with reference only to whichever axis of the eye has been reversed. When this is done in adult newts and salamanders, the retina of the transplanted eye undergoes degeneration and a new retina and optic nerve are regenerated. Nevertheless, functional recovery is the same.

In another type of experiment, the optic nerve of one eye has been cross-united with the contralateral nerve so that the regenerating fibers hook up with the wrong side of the brain. After recovery, such animals respond as if everything seen with one eye were being viewed through the contralateral eye. Under these conditions and in all the foregoing, the various retinal points retain their particular central associations within the optic tectum in a systematic, predetermined manner, despite the intermingling of fibers on their way into the brain and despite the adverse functional effects produced by surgical rearrangement of the normal relations between center and periphery.

A restoration of maladaptive functions can hardly be ascribed to learning or to other forms of functional adaptation. Hence, functional adjustment may be discarded along with mechanical guidance and orderly timing of fiber ingrowth as possible explanations of the patterning of central synapses. Comparison of the scotomata produced by lesions in the optic tectum in normal animals with those produced after optic nerve regeneration indicates an orderly restoration of retinal projection in the anatomical as well as functional sense.

From this and similar evidence we have been able to draw the following tentative conclusions: The fibers of the optic nerve must differ from one another in their constitutional (presumably chemical) properties. This fiber specificity, furthermore, must follow an orderly plan in that it must reflect the topography of the retinal field, each fiber being specified according to the particular locus of the retinal field from which it arises. In order that each retinal locus may have its unique properties, the retinal field must undergo differentation with refer ence to at least two different axes, e.g., anteroposterior and dorsoventral. There probably is additional differentation along the mediolateral axis as well .Were the optic fibers all alike, there would be no means, following their mix-up in the nerve scar, by which they could be distinguished from one another in the centers and their differential functional relations restored.

We have suggested that this fiber specificity probably arises through a polarized differentiation of the retina or its anlage in development, the specificity then being extended from the retinal ganglion cells into their axonal prolongations. Accordingly, it was predicted that if retinal inversion were to be performed sufficiently early, i.e., before polarization had been rigidly determined, normal instead of reversed vision should follow. The possibility was also pointed out that the anteroposterior and dorsoventral axes of the retina may be determined at different stages of development, as in the limb bud, in which case contralateral transplantation of the eye anlage might be expected to produce inverted vision at earlier stages following anteroposterior inversion, for example, than after dorsoventral inversion. Follow-up study of

some of these embryological aspects of inverted vision (Stone, 1944, 1948) appear to be confirmatory as far as they have gone.

It has been possible to deduce further that the second-order tectal neurons with which the optic fibers make synapsis are likewise subject to a refined specification that is correlated with the topography of the optic tectum. Again, if the central neurons were all alike, there would be no means by which the proper patterning of central synapses could be controlled. The tectal specification is presumed to arise through central self-differentiation of the optic lobe.

Finally, since the adjustment of the central relations must be determined with reference to these neuronal specificities, it follows that the formation of synaptic connections must be regulated on some sort of chemo-affinity basis. We may picture the optic fibers, as they invade the optic lobe, encountering many different elements: capillaries, glia cells, axons of other afferents, and the numerous dendrites and cell bodies of the tectal neurons. Not all contacts made by the growing fiber tips result in the formation of synaptic endings. In most cases the growing tips continue to push on beyond the various elements they encounter. It is only when a fiber happens to contact a nerve dendrite or soma, the chemical constitution of which specificially matches that of the invading fiber, that a specialized synaptic ending is formed and further growth of that fiber tip ceases. For each retinal locus we assume a corresponding focal area in the optic lobe. Fibers arising from a given point of the retina have a predetermined, selective affinity for the neurons of the corresponding central locus.

Thus, we conclude that the central reflex relations of the optic nerve, instead of being patterned by electrical or other effects of function, or through a scheduled timing for fiber ingrowth and stereotropic guidance, are determined rather on the basis of interneuronal affinities and incompatibilities of a chemical or physico-chemical nature. These latter are products primarily of embryonic cell differentation and for the most part arise independently of function. With certain qualifications and additions, our conclusions fall within the framework of the old ideas of Cajal (1929), Tello (1923), and others on neurotropism and chemotaxis which, along with those on galvanotaxis, have generally lost prestige in recent decades owing to emphasis on stereotropic factors in nerve growth.

In the visual system the sensory ganglion cells lie embedded within the end-organ itself. In other cranial and spinal nerves the cell bodies of the sensory neurons are located within separate ganglia, only the tips of the sensory fibers being in direct contact with the end-organ tissue. The specification of the sensory fibers, therefore, must typically be achieved on a somewhat different and more complicated plan than that observed in the visual system. The more typical conditions are illustrated in the development of cutaneous local sign.

It is a common capacity of the vertebrates to be able to localize with considerable accuracy and without aid of vision a cutaneous stimulus, like a pin-prick, occurring anywhere on the body. Even fish are capable of some localization of this kind. The common catfish is said to localize taste as well as tactile stimuli over the entire body surface. There is something about the excitations entering the brain from different points on the cutaneous covering that indicates the locus from which the excitations arise. This is known as the "local sign" quality of cutaneous sensibility.

These local sign properties depend upon the central connections of the cutaneous fibers. This is clearly demonstrated by the false reference of sensations that follows misregeneration of cutaneous fibers into foreign regions of the integument. For accurate localization, it is necessary that the peripheral connections of the cutaneous neurons match perfectly the central connections with reference to the topography of the entire body surface.

We have been interested in recent years in the problem of how this neat adjustment between periphery and centers is brought about in development. The localizing responses of the frogs and

newts have been found to be sufficiently developed to serve as criteria for study of the ontogeny of cutaneous local sign. As in the visual system, it has been possible to demonstrate that the central connections are not patterned on the basis of an orderly plan in the timing and mechanical guidance of sensory fiber ingrowth. Normal reflex patterns are systematically restored in centripetal regeneration of the sensory roots (Sperry and Miner, 1949; Sperry, 1950a.) This is the case even when the regenerating fibers have been forced to enter the brain over the pathways of a foreign nerve root.

It has been possible to show also that, in the amphibians at least, the central synapses are not patterned through processes of functional adaptation. For example, after contralateral cross-union of the ophthalmic nerves in frog tadpoles, the metamorphosed frogs consistently wipe off the right side of the snout when the left side is stimulated. After transplantation of skin flaps across the midline of the back in frog tadpoles, the metamorphosed frogs continue to wipe erroneously at the original site of the skin flap using the leg on the opposite side of the body. After cross-union of ophthalmic and mandibular nerves in newts, the recovered withdrawal responses to stimulation of the mandible are reversed pressing the skin against the stimulating object instead of pulling it away. After contralateral cross-union of the dorsal nerve roots of the hind limb in frog tadpoles, the metamorphosed frogs make characteristic, but useless and maladaptive responses of the left limb instead of the right when the right foot is stimulated.

In all these cases the central synaptic connections are formed in predetermined fashion according to the usual systematic plan. The synaptic patterning cannot be attributed to functional adaptation in these instances, however, because the various surgical rearrangements have rendered the synaptic patterns maladaptive. Although it has been commonly thought that cutaneous local sign in the higher vertebrates is something that is acquired by experience, there is contradicting evidence (Sperry, 1943a; 1945c) indicating that in the mammals as well and even in man it is based upon an inherent organization patterned through developmental forces.

It has been necessary to conclude that there exists a chemical specificity among the sensory cutaneous neurons which parallels closely their functional differentiation. Specification of the central neurons also has been a necessary inference. The patterning of reflex associations, therefore, seems to be regulated in the cutaneous, as in the visual, system by selective chemoaffinities between the central and peripheral nerve cells.

There remains the problem of the adjustment of the peripheral connections in the skin and how these are made to match correctly the specific properties of the sensory neurons and thereby their central connections. In order to explain this, we have to infer that the integument itself is subject to an extremely refined local specification. Each cutaneous locus must have its own unique chemical properties. This could be attained through a graded, field-like specification of the integument, without necessitating any mosaic or punctiform type of specificity.

Assuming this specification of the integument, it becomes possible to account for the adjustment of the peripheral connections. One might postulate, for example, a selective outgrowth of the different fiber types, each to its appropriate cutaneous locus. This possibility, however, has been contradicted by the evidence in favor of an alternative. The actual data (Miner, 1950) indicate that the cutaneous fibers grow out and connect with the integument largely at random within the body segments, after which the differentiation of the integument induces a corresponding specificity in the attached nerve fibers according to the locations of their cutaneous contacts. Thoracic nerves that normally innervate the skin of the back and trunk of the frog can be forced, by limb-bud transplantation and other means, to grow into and innervate limb skin. Under these conditions the *thoracic* nerves will establish central reflex relations appropriate for the peripheral *limb* connections. Instead

of the typical responses aimed at the back or trunk, stimulation of such thoracic fibers elicits responses characteristic of limb stimulation.

The experiments so far have shown that the developing cutaneous nerves will readily innervate atypical cutaneous areas, and that the type of central reflex relations which are formed depends upon the type of integument with which the nerves connect in the periphery. When we put together the foregoing findings, we can begin to account for the way in which each cutaneous point manages to acquire its proper "local sign" and how the overall map of the body surface gets projected, so to speak, into the central circuits without aid of functional adjustment.

In addition, the cutaneous circuits must necessarily be neatly integrated with the mechanisms mediating kinesthesis and posture sense. A given cutaneous point on the back of the hand in man, for example, may be perceived at any one of almost an infinite number of points in space depending upon the posture of the arm at the time. Retinal local sign is subject to the same complication. Although somewhat simplified, similar integration is present in the frog. Responses elicited from a given cutaneous point vary also with reference to other factors. For example, withdrawal reactions in a frightened animal may undergo a complete reversal to become positive approach responses if the animal is no longer frightened, but is hungry.

In our discussion of the development of the visual and cutaneous pathways, several features have been illustrated which appear to have rather wide applicability for the establishment of central-peripheral relationships, in general. The refined, local differentiation of the endorgan tissues, and the correlated neuronal specification through endorgan contacts were first demonstrated for the limb musculature and its innervation (Weiss, 1936; 1941). They have since been reported for the extrinsic musculature of the eye and the endorgans of the labyrinth, as well as for the retina and integument. We now believe the same holds true for all other organs and tissues in which local sign sensibility or differential motor function is present, for example, the tendons, joints, fascias, periosteum, and the various viscera.

Along with the foregoing, the influence of the peripheral associations upon the patterning of central synapses, as illustrated in the visual and cutaneous pathways, appears to be a general principle in neurogenesis. We have referred to this as the "peripheral regulation of central synapsis."

In general, the differentiation and refined specification of the endorgan tissue leads the way in development. Specification is then secondarily induced in the nerve fibers by the endorgan contacts they happen to form. In this way the differentiation of the periphery becomes projected along the peripheral nerves into the centers and thereby the proper central hook-ups with the peripheral endings is made possible.

Another point illustrated in the examples, is the central self-differentiation of the second and higher-order neurons within the central nuclei. The neurons of the primary sensory nuclei appear to undergo differentiation, in some cases, according to the anatomical relations and dimensions of the nuclear structure itself, as in the optic tectum. In other cases, the central neurons are more scattered and presumably their specification is more dependent upon their efferent associations.

The two types of neuronal specification mentioned above, i.e., intrinsic self-differentiation, on the one hand, and that attained through contact with other cells by extrinsic inductive actions, on the other, are not as distinctly separable as might be inferred from our abbreviated discussion. The final specificity of many neurons must depend upon the summated result of both processes. For example, the primary cutaneous neurons presumably undergo a certain amount of self-differentiation prior to and independently of the peripheral effects. A rostro-caudal differentiation of the sensory ganglia along the neuraxis probably precedes any peripheral contacts. The modal differentiation into pain, tactile and thermal neurons also may be independent of the peripheral contacts. Local specificity we

view as a late refinement superimposed upon these grosser differentiations.

The preceding statements concerning random outgrowth of peripheral nerves are, likewise, subject to some qualification. Peripheral nerve outgrowth is by no means entirely fortuitous. Selectivity is imposed in a varying degree by the mechanical restrictions of nerve outgrowth and also by the modal characteristics of the various neuron types. Outgrowth and termination appear to be selective at least to the extent of preventing mix-ups, for example, between motor and sensory fibers, or between cold, tactile, proprioceptive, and taste fibers, etc.

Thus far we have dealt primarily with the adjustment of peripheral connections and of synaptic associations in the primary motor and primary sensory nuclei. You may ask whether the same principles apply at all to the patterning of synaptic relations in the more central portions of the integrative circuits, i.e., in the secondary and tertiary nuclei and in the various higher association centers of the brain. What evidence we have thus far indicates that this is the case. Experiments involving regeneration of the long intracentral association tracts linking the midbrain, diencephalon, and forebrain with the lower centers of medulla and cord have yielded results consistent with those above. We find that the formation of these intracentral synaptic associations takes place in the usual orderly fashion despite mechanical intermixing of the fibers and despite resultant maladaptiveness in function.

The evidence would seem now to be sufficiently extensive to warrant the conclusion that the developmental patterning of synaptic linkages is regulated on these same principles throughout the nervous system. If we put together the experimental evidence now available regarding the patterning of neuronal connections for the primary sensory, the primary motor, and the intracentral neurons, it becomes possible to draw up a working picture of the development of the complete reflex pathway. This we are now able to do for the optokinetic reflexes, the vestibulo-ocular reflexes, the myotatic (tendon, or muscle-stretch) reflexes, and some of the cutaneous reflexes.

In summary, it appears that the nervous system during development undergoes a refined differentiation or specification in which the individual neurons gradually acquire specific constitutional properties. This is achieved in part by intrinsic self-differentiation, particularly within the centers, and in part by inductive effects imposed through distant fiber contacts. As the elongating processes of the developing neurons begin to invade and to ramify within the neighboring and distant synaptic regions of the neuraxis, the formation of synaptic linkages does not, even at the beginning, proceed in any promiscuous fortuitous, or equipotential fashion. Synaptic association is not established between any and all neurons that happen to make contact. Only when a nerve fiber encounters another neuron the chemical properties of which are specifically suited to those of the growing fiber, does establishment of the intimate and lasting synaptic union result.

The fact that the distribution of neuronal specificities in the growing embryo and the resultant patterns of synaptic linkage turn out to be functionally adaptive for the organism is explainable, like other organ adaptations, in terms of evolutionary selection. Our attempts to analyze the direct mechanisms by which this adaptive patterning is assured in the developmental process itself, have been applied thus far only to some of the simpler sensory-neuro-motor relations.

The question always arises: To what extent are our findings in the lower vertebrates applicable to the higher mammals, including man? In general, we can only answer that the embryonic processes are known to show greater constancy in evolution than do adult characteristics. We have no reason to suppose that any radical revolution has occurred in phylogeny in the methods and principles used in assembling the basic integrative architecture of the vertebrate nervous system. That there has been considerable refinement and alteration in the details of their application, on the other hand, is to be expected. In particular, the part played by learning in patterning the

neural circuits increases tremendously in the higher primates and man. Insofar as we can tell at present, this change seems to be a matter, not so much of substituting learned circuits where inherent circuits previously prevailed, as of adding new brain structures for regulation of the more primitive circuits and final common pathways. These new additions, in which the organization is dependent to a much greater extent upon function and the learning process, seem in large part to be superimposed upon the older integrative mechanisms. However, even in man all the complicated interconnections of the nervous system including those of the cerebral cortex, now known to neuroanatomy, insofar as they are typical of the species, must be regarded as products of developmental forces such as those we have been discussing. Any patterning produced by the learning process has yet to be demonstrated anatomically.

Brief consideration of the problems of neural development will reveal that so far we have only begun to scratch the surface. There remains a tremendous amount of detail yet to be filled in before we shall have anything like a complete analysis of the developmental organization of even the simpler polysynaptic reflex pathways.

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